TREATING TRAUMATIZED CHILDREN

Clinical Implications of the Psychobiology of Posttraumatic Stress Disorder

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There is growing evidence that child maltreatment and posttraumatic stress disorder result in numerous neurobiological alterations in children and adolescents, including abnormalities in brain structure and functioning. This article reviews several psychobiological systems with regard to their functioning under normal stress and in the presence of posttraumatic stress disorder, with a focus on recent research findings in children and adolescents, and the implications these findings have on clinical intervention for traumatized children. The importance of early identification and treatment of traumatized children and the need to empirically evaluate psychopharmacological interventions for childhood posttraumatic stress disorder are discussed in detail. Research and policy priorities are also addressed.

Key words: *posttraumatic stress disorder, children, adolescents, psychobiology, psychopharmacology, treatment*

RECENT RESEARCH has greatly increased our understanding of the psychobioogical changes that accompany posttraumatic stress disorder (PTSD). Although most of this research has been conducted with adults, there are a growing number of studies that have examined these outcomes in traumatized children. This new research has made it clear that PTSD is a particu-

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larly complex disorder that involves many different physiologic systems. This is not surprising if we consider that the very survival of living organisms depends on their ability to cope with and adapt to stress. Thus, the human species has evolved to maintain homeostasis (stability of bodily functions) in the face of a wide variety of stressors. These include environmental stressors such as changes in temperature or food availability, internal biological stressors such as childbearing, aging or illness, and external threats such as natural disasters or the presence of predators.

Under most circumstances, human beings utilize exquisitely complex and fine-tuned mechanisms to adjust to these and other stressors. However, there is a limit to the amount of stress that any organism can adapt to while maintaining homeostasis. Beyond that point, the very psychobiological mechanisms that typically allow us to function well under stress may act in ways that contribute to, maintain, or even cause disease (Selye, 1973). Thus, children who have experienced severe stressors may develop PTSD or other illnesses that indicate that the person's stress adaptation systems have been acutely or chronically overwhelmed. Having an understanding of how these systems typically respond to stress, and how they function in the presence of PTSD, may contribute to our ability to design and deliver more optimal treatments to traumatized children. This article reviews what we currently know about the psychobiology of PTSD in children and how this knowledge can guide our efforts to provide these children with the best possible treatment.

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Because our response to stress involves so many biological systems reacting and interacting simultaneously, it is less confusing to examine each system separately rather than to try to describe these reactions according to their sequential time course. For this reason, we will describe each biological stress system's reaction to normal stress, that system's functioning in adults with PTSD, what we know about how that system operates in children with PTSD, and the clinical treatment implications of this information. The interested reader can find more detailed descriptions of the neurobiology of PTSD and traumatized children elsewhere (DeBellis, in press; DeBellis & Putnam, 1994).

KEY POINTS OF THE RESEARCH REVIEW

- Several studies have indicated psychobiological abnormalities in adults and children with posttraumatic stress disorder.
- These studies suggest the utility of a variety of psychosocial and psychopharmacologic interventions for traumatized children.
- Although trauma-focused cognitive behavior therapy has been found to be efficacious for children exposed to various types of trauma, no controlled medication trials have been conducted for children with posttraumatic stress disorder.
- Because adult pharmacologic treatment findings may not apply to children, controlled medication trials for traumatized children are needed.
- Posttraumatic stress disorder has been found to be associated with abnormalities in a variety of brain structures and functions in adults and children.
- Understanding the psychobiological alterations that occur in normal stress and in posttraumatic stress disorder can guide treatment development for traumatized children.
- There are theoretical reasons to indicate that both psychosocial and pharmacological interventions may be indicated for optimal treatment of posttraumatic stress disorder symptoms to children and adolescents.
- It is likely that different treatment approaches will be optimal for different traumatized children, depending in part on which symptoms are most prominent or troublesome.
- More research is needed to determine the psychobiological consequences of childhood traumatization and optimal treatment approaches for this population.

THE AMYGDALA AND MEDIAL PREFRONTAL CORTEX

Normal Stress Response

The amygdala is part of the brain's limbic system, which is involved in modulation and expression of emotions. We initially perceive external stimuli through our sensory organs; information that we see, hear, touch, or smell is transmitted through neural connections to the amygdala. The amygdala integrates this sensory information for storage in and retrieval from memory. It also attaches emotional valence to the received sensory information and then transmits this information to all the other systems involved in the stress response. Specifically, the amygdala has direct connections to the locus ceruleus, which initiates the noradrenergic (norepinephrine) stress response; to the paraventricular nucleus of the hypothalamus, which initiates the stress-sensitive hypothalamic-pituitary-adrenal axis; to the vagus nerve and medulla of the brain, which are responsible for stress-induced increases in heart rate and blood pressure; to the parabrachial plexus, which leads to increased respiratory rate during stress; to the central gray matter of the brain, which is involved in conditioned fear, the phenomenon of "freezing" during acute stress and stress-induced analgesia; and to the nucleus reticularis pontis caudalis, which controls fear-related heightening of the startle reflex. Thus, the amygdala serves as an initial screening center for sensory input that, if perceived as stressful, triggers a cascade of physiologic and psychologic responses.

The amygdala is also neurally connected to the medial prefrontal cortex. This area of the brain is involved in planned behaviors, working memory, motivation, and distinguishing between internally versus externally derived models of the world (Knight, Grabowecky, & Scabini, 1995). Very relevant to PTSD is the fact that part of the medial prefrontal cortex, the anterior cingulate, is also important in extinguishing learned fear responses.

The medial prefrontal cortex normally releases several neurotransmitters (chemicals that promote intraneural activity and communication), including dopamine, norepinephrine, and serotonin, all of which will be discussed in detail below. In the typical stressful situation, release of these neurotransmitters results in negative feedback to the amygdala. Negative feedback means that a specific substance has an inhibitory effect on the organ that stimulated its original release—in other words, increased presence of that substance serves to limit further release of itself, thereby preventing a situation in which there would be too much of that substance. This negative feedback loop is a common mechanism the body uses to maintain homeostasis.

Functioning in PTSD

It has been postulated that PTSD may in part be the result of hyperresponsiveness of the amygdala. The resultant overstimulation of all of the stress systems connected to the amygdala could explain many of the symptoms associated with PTSD. Because the amygdala itself is directly involved in attaching emotional valence to sensory information and the encoding, storage, and retrieval of emotional memories (Eichenbaum & Cohen, 2001), overreactivity of the amygdala might explain the recurrent and intrusive traumatic memories as well as the excessive fear associated with traumatic reminders that are hallmarks of PTSD. Evidence from recent studies has provided direct support for this idea. For example, researchers have demonstrated that adults with combat-related PTSD have greater activation of the amygdala in response to both nonspecific fear stimuli and combat-specific stimuli than healthy adult subjects without PTSD (Liberzon et al., 1999; Rauch et al., 2000). Because the amygdala is also involved in memory, particularly emotional memory processing, it is relevant that adults with PTSD do more poorly than control subjects on tests of explicit memory of trauma-related words (Bremner et al., 1993). Children with PTSD also perform more poorly on memory tasks (Moradi, Doost, Taghavi, Yule, & Dalgleish, 1999) and have a memory bias for negative words compared to healthy child control subjects (Moradi, Taghaiv, Neshat-Doost, Yule, & Dalgleish, 2000). Although these findings do

not specifically implicate the amygdala, they are consistent with the hypothesis of amygdala dysfunction in PTSD.

In contrast to the hypothesized overreactivity of the amygdala, it appears that the medial prefrontal cortex may be underreactive in PTSD. In support of this theory, presentation of traumatic words or scenarios resulted in significantly less blood flow and neuron activity in the medial prefrontal cortex and anterior cingulate in adults with PTSD than in adults without PTSD (Bremner et al., 1999; Shin et al., 1999). As will be discussed below, it is possible that this deactivation of the medial prefrontal cortex is due to an excess of dopamine. The persistence and overgeneralization of conditioned fear responses seen in childhood PTSD may thus be due to the decreased activity of the medial prefrontal cortex, which normally extinguishes these responses.

Clinical Significance

Thus in PTSD, there appears to be an overactivation of the brain area responsible for assigning emotional meaning to sensory stimuli and encoding emotional memories (the amygdala), and possibly underactivity of the brain area involved in extinguishing learned fear responses (anterior cingulate of the medial prefrontal cortex). These abnormalities may cause or contribute to core PTSD symptoms, including increased and intrusive traumatic memories (flashbacks or nightmares) and the extreme and sometimes inappropriate fear that is associated with these traumatic reminders. This suggests that in treating traumatized children, and particularly those with full-blown PTSD symptoms, it is important to include psychological interventions that target the deficits caused by these brain abnormalities. Interventions that help the child to assign appropriate emotional meaning to the traumatic experience as well as to events experienced in daily life, and that help extinguish learned fear responses, may be essential for full remission of PTSD symptoms.

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Trauma-focused cognitive-behavioral therapy (CBT) currently has the most scientific evidence of efficacy in decreasing PTSD symptoms in traumatized children (Cohen, Berliner, & March, 2000). This treatment model includes two specific components (cognitive processing and exposure) that directly address the deficits discussed above. Specifically, cognitive processing teaches the child to examine and reframe the "meaning" of the trauma and other experiences, whereas exposure techniques decondition the child's learned fear reactions to thoughts and discussions about the trauma. Thus, it is possible that CBT may, for example, correct the exaggerated emotional valence an overreactive amygdala assigns to traumatic reminders and reverse conditioned fear responses that the anterior cingulate would normally extinguish but fails to do in the presence of PTSD. Although no studies to date have examined whether these two components are the CBT "essential ingredients" for resolution of PTSD symptoms, more generic interventions that lack these components have not been as successful at decreasing PTSD symptoms in traumatized children. This lends credence to the suggestion that therapists should incorporate these elements of CBT into their interventions for traumatized children whose intrusive and fear symptoms persist in the face of other types of treatment (Cohen, Berliner, & Mannarino, 2000). It is possible that CBT may be unable to overcome the effect of severe brain dysfunction and thus may be ineffective for some children with extreme neurobiological abnormalities.

DOPAMINE SYSTEM

Normal Stress Response

Dopamine (DA) is a neurotransmitter involved in several functions of the central nervous system (CNS) including pleasure-seeking

and reward behaviors; paranoid ideation and hypervigilance; addiction to ethanol, cocaine, nicotine, and opiates; movement disorders such as Parkinsonism and extrapyramidal side effects of many medications; and inhibition of prolactin release.

DA affects brain functioning primarily by modulating the actions of other neurotransmitter systems. These interactions are complex and in some cases speculative in terms of DA's activity in response to stress. However, it is clear that stress results in increased DA acting on the prefrontal cortex. It is believed that the amygdala, through excitatory actions of another neurotransmitter, glutamate, stimulates release of DA from the prefrontal cortex and from other DA storage sites in the brain (Chambers et al., 1999). Through negative feedback, DA then dampens the glutamate effect on the prefrontal cortex and perhaps has direct negative feedback to the amygdala, inhibiting further stimulation of the prefrontal cortex, thus tending to maintain homeostasis. DA also inhibits prefrontal cortex activity by stimulating release of the inhibitory neurotransmitter GABA. There are preliminary data to suggest that stress-induced release of DA in the prefrontal cortex is involved in developing appropriate coping responses to stress (Deutch & Young, 1995).

Functioning in PTSD

It has been hypothesized that in PTSD, there is an excessive amount of DA acting on the medial prefrontal cortex. In this situation, these persistently high DA concentrations would simultaneously inhibit the excitatory glutamate effect and enhance the inhibitory GABA effect on the prefrontal cortex, leading to an underfunctioning of this brain area. As discussed above, decreased prefrontal cortex functioning leads to an inability to extinguish conditioned fear responses. Thus, an excess of DA may contribute to the persistent and overgeneralized fear characteristic of PTSD. Indeed, many PTSD patients have hypervigilance or paranoia, which are characteristically seen in hyperdopamine conditions.

There is evidence of increased DA presence in both adults and children with PTSD. DeBellis and colleagues (DeBellis, Baum, et al., 1999; DeBellis, Lefter, Trickett, & Putnam, 1994) demonstrated significant increases of DA and its metabolite in the urine of sexually abused girls and of maltreated girls and boys with PTSD, and that the severity of PTSD symptoms was positively correlated with the amount of DA in these children's urine.

Clinical Significance

If an excess of DA is responsible for some PTSD symptoms, an agent that blocks the synthesis or action of DA may reverse this process and lead to an improvement in PTSD symptomatology. Several medications that decrease DA activity in the brain are available, and some of these have been used to treat PTSD symptoms. For example, neuroleptic (antipsychotic) medications are DA antagonists (i.e., they block the activity of DA in the brain). One study of an atypical antipsychotic, risperidone (Risperdol), was used in an open trial (i.e., without a control group) for 18 boys with severe PTSD symptoms. Thirteen of these children experienced a remission of PTSD symptoms with this treatment (Horrigan & Barnhill, 1999). However, there have been no controlled studies with adults or children to indicate the efficacy of this treatment, and at this time antipsychotic medications are not considered a first-line pharmacologic treatment for PTSD. Recent treatment recommendations indicate that these agents may be useful in patients who have hypervigilant or paranoid symptoms or are highly agitated or psychotic (Friedman, Davidson, Mellman, & Southwick, 2000, p. 101). It is interesting to note that the study that found risperidone to be efficacious in childhood PTSD predominantly treated children with comorbid attention deficit hyperactivity disorder (85%) or bipolar disorder (35%), and therefore may have had high rates of agitation or psychosis (Horrigan & Barnhill, 1999). An additional concern for these children may be that they have increased rate of familial mood disorders, which predicts increased sensitivity to tardive dyskinesia (a serious side effect of

antipsychotics). Therefore, caution should be exercised in using these agents in traumatized children.

Another class of medication, the selective serotonin reuptake inhibitors (SSRIs), also suppresses release of DA from the substantia nigra (the primary DA storage site in the brain) and may thus be useful in treating PTSD symptoms. Although none of the SSRI medications have been tested in childhood PTSD, some have been found to improve PTSD symptoms in placebo-controlled trials in adults, and two SSRI medications, sertraline (Zoloft) and paroxetine (Paxil), have recently become the first medications to receive FDA approval for the treatment of adult PTSD. However, it is not clear whether the DA-blocking activity of these medications (as opposed to their effect on serotonin) is responsible for any of the clinical improvements noted. The finding that one medication, buproprion (Wellbutrin), which minimally increases DA availability, has been successful in treating some adult PTSD symptoms is probably related to its metabolites' effect of increasing norepinephrine, which is much stronger than its effect on DA (Frazer, 1997). Although any potential pharmacologic treatment for PTSD requires well-controlled studies to elucidate effectiveness, an understanding of the potential role of DA in childhood PTSD may thus contribute to the optimal selection of which medications to test.

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NOREPINEPHRINE/ EPINEPHRINE (ADRENERGIC) SYSTEM

Normal Stress Response

The norepinephrine/epinephrine system is the best-understood stress response system. (It is called the "adrenergic system" because the British terms for *epinephrine* and *norepinephrine* are *adrenaline* and *noradrenaline*, respectively.) Although norepinephrine (NE) acts as a neurotransmitter both in the CNS and peripherally, epinephrine (Epi) only acts peripherally. Stress increases the responsiveness of the locus ceruleus, the main site of NE production and storage in the brain. This results in increased NE production and output in the amygdala, prefrontal cortex, hypothalamus, and hippocampus. Stress also directly activates the sympathetic nervous system (SNS). The SNS controls the "fight-or-flight" response, during which there is heightened anxiety, arousal, and vigilance for expected imminent danger. Physiologic changes during SNS activation include increased heart rate, blood pressure, metabolic rate and alertness, sweating, and blood coagulation (useful if one is injured by a predator); and blood flow away from the skin, gut, and kidneys and toward the heart, brain, and skeletal muscles (useful for running away from the predator). These responses have been observed under a wide variety of stressful conditions in both adults and children.

Functioning in PTSD

There is evidence that the adrenergic system exhibits maladaptive functioning in adults with PTSD and in traumatized children with or without full-blown PTSD. In these populations, there is evidence of increased adrenergic tone, which is the system's baseline function, as measured in 24-hour collections of NE, Epi, and their metabolites. In addition, there is evidence of increased sensitivity to stress (reactivity); for example, increased heart rate and blood pressure when exposed to traumatic reminders as compared to non-PTSD control subjects. Several studies in children have demonstrated increased NE, Epi, and/or their metabolites in 24-hour urine collections of depressed neglected boys, sexually abused girls with depressive symptoms, and boys and girls with abuse-related PTSD (DeBellis, Baum, et al., 1999; DeBellis, Lefter, et al., 1994). Another study found that physically and sexually abused children with PTSD had greater increases in heart rate when exposed to a physio-

logic challenge than did non-PTSD control children (Perry, 1994). This increased SNS tone and hyperreactivity of the adrenergic system to stress may account for many of the hyperarousal symptoms (sleep difficulties, motor hyperactivity) seen in children with PTSD.

Clinical Significance

Relaxation techniques including progressive muscle relaxation, positive imagery, and focused deep breathing such as that used in yoga, can significantly lower blood pressure and heart rate in medically ill adults through what has been described as the "relaxation response" (Benson & Klipper, 2000). Although no studies have demonstrated the specific effect of using these techniques in traumatized children, most published trauma-focused CBT manuals for children include the use of these relaxation techniques (Cohen & Mannarino, 1993; Deblinger & Heflin, 1996; March, Amaya-Jackson, Murray, & Schulte, 1998). They have anecdotally been noted to help such children fall asleep at night (Cohen & Mannarino, 1993) and may be important in decreasing other hyperarousal symptoms as well. Although more research is needed to test the specific efficacy of such relaxation techniques, clinicians should become proficient in using these techniques and consider their use with traumatized children, particularly those with prominent hyperarousal symptoms.

There are different kinds of adrenergic receptors in the body (called alpha or beta receptors). Several medications decrease adrenergic transmission (i.e., they block the action of NE or Epi), and some have been found to decrease PTSD symptoms. Clonidine (Catapres) is a postsynaptic alpha adrenergic blocker and has been found in open (noncontrolled) studies to decrease basal heart rate, anxiety, impulsivity, and hyperarousal symptoms in children with PTSD (Harmon & Riggs, 1996; Perry, 1994). In one case study, Clonidine treatment resulted in improved sleep and increased neural integrity of the anterior cingulate (DeBellis, Keshavan, & Harenski, 2001; DeBellis, Keshavan, Spencer, & Hall, 2000). Propranolol (Inderal) blocks beta adrenergic receptors and has been found in one open study to decrease reexperi- encing and hyperarousal symptoms in children with PTSD (Famularo, Kinscherff, & Fenton, 1988). It should be noted that significant negative side effects may limit the utility of using Clonidine or Propranalol in pediatric populations. Over time, tricyclic antidepressants (TCAs) such as imipramine (Tofranil) also decrease reactivity of beta adrenergic receptors. However, because of rare but serious side effects, TCAs have recently fallen out of favor for first-line use in child and adolescent psychiatric disorders. Controlled trials are needed to confirm whether any of these medications are useful in decreasing PTSD symptoms in children, but the available evidence indicates that they may be helpful in children with significant hyperarousal symptoms. Given the fact that all medications have some side effects, it may be preferable to try relaxation techniques prior to initiating a medication trial to reduce these symptoms.

HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

Normal Stress Response

As noted above, stress activation of the amygdala results in stimulation of the paraventricular nucleus of the hypothalamus. This organ then releases corticotropin release factor (CRF), also called corticotropin release hormone (CRH). The anterior pituitary gland has CRF receptors which, upon detecting increased CRF, stimulate the pituitary to release corticotropin (ACTH). ACTH receptors in the adrenal cortex respond to ACTH by stimulating release of cortisol. Cortisol is a hormone that leads to increased synthesis of glucose in the liver (necessary for optimal brain functioning) and decreases the availability of glucose to skeletal muscles (Bentley, 1985, p. 152). Cortisol also dampens the normal immune response and the release of growth hormone (which may be helpful for survival in an acutely threatening situation). Under normal stress, an elegant negative feedback system, whereby each hormone

causes a decrease in its own production and release, maintains homeostasis. Specifically, the amygdala responds to increased levels of CRF by decreasing stimulation of the hypothalamus, the hypothalamus responds to increased levels of ACTH by decreasing the output of CRF, the pituitary responds to increased levels of cortisol by decreasing the output of ACTH, and cortisol also has negative feedback to the amygdala and the hypothalamus. This negative feedback is mediated by cortisol receptors in the amygdala, hypothalamus, and pituitary, which are sensitive to changes in cortisol concentration and induce neuronal transmission in response to these changes. If the acute stress is severe enough or if it continues, the cortisol receptors may actually decrease in numbers, resulting in lower sensitivity to cortisol. This could lead to ongoing hypothalamic hypersecretion of CRF and/or pituitary hypersecretion of ACTH, leading to abnormally high cortisol levels. In fact, this has been found in people exposed to acute severe stress (DeBellis, Chrousos, et al., 1994).

The overriding implication of these findings is that psychobiological responses to stress change over time and may become increasingly maladaptive the longer they persist. Thus, although children evaluated soon after abuse is reported appear to be similar physiologically to children with a normal acute stress response, those with longstanding PTSD have signs of chronic physiologic abnormalities, even in the absence of new stressors.

Functioning in PTSD

There is evidence that in some adults with chronic PTSD (such as combat veterans or Holocaust survivors), there are elevated levels of CRF in the brain but decreased levels of ACTH or cortisol. This suggests a disconnect between CRF, ACTH, and cortisol in chronic PTSD. This is believed to be the result of enhanced negative feedback of cortisol on the HPA axis (Yehuda, Giller, Southwick, Lowy, & Mason, 1991). The long-term result of this is low baseline cortisol and a dampened cortisol response to a new acute stress (Yehuda, 1999). However, other groups of adults with longstanding PTSD have been shown to have increased baseline cortisol (Lemieux & Coe, 1995). It is possible that hormone-based gender effects or differences in methods used to measure cortisol account for these variable findings; in particular, estrogen affects cortisol level, and estrogen status has not been well-controlled for in most studies (Brady, 2001; Rasmussen & Friedman, in press).

In children, the interaction of stress and the HPA axis appears to be complex. Children with acute traumatic exposure (for example, sexually abused children tested within 6 months of abuse disclosure) show hypersecretion of cortisol (DeBellis, Baum, et al., 1999; Hart, Gunnar, & Cicchetti, 1996; Kaufman, 1991). In contrast, children with longstanding PTSD (i.e., those abused or otherwise traumatized in the past, with no ongoing acute stressors) were found in one study to have blunted ACTH response to CRF challenge, suggesting that CRF hypersecretion had led to an adaptive decreased number of CRH receptors in the anterior pituitary; that is, enhanced negative feedback similar to that seen in many adults with chronic PTSD (DeBellis, Chrousos, et al., 1994). Similarly, low baseline cortisol levels were found in children exposed 5 years previously to an Armenian earthquake (Goenjian et al., 1996). However, children with ongoing or new stressors in addition to a past history of maltreatment were found to have increased ACTH response and CRH levels but normal cortisol response in one study (Kaufman et al., 1997). Thus, it appears that there are different patterns of HPA axis abnormalities in PTSD, which may be related to the length of time since the original trauma exposure as well as whether the child has had subsequent traumatic experiences.

Clinical Significance

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chronic physiologic abnormalities, even in the absence of new stressors. This provides compelling support for the need for traumatized children to be identified and treated early. Unfortunately, there is evidence that both traumatic exposure and PTSD are underidentified and undertreated in children and adolescents (Steiner, Garcia, & Matthews, 1997). Screening for traumatic exposure in routine settings such as pediatric offices or schools has been recommended elsewhere (Cohen, Berliner, & Mannarino, 2000). Even among mental health care providers, screening for traumatic exposure and PTSD may be less than optimal. All child therapists, even those who do not specialize in treating traumatized children, should develop proficiency in this regard. The apparently progressive nature of the psychobiological alterations in HPA axis functioning suggests that, when children are identified as having significant PTSD symptoms, even if they do not meet full criteria for this disorder, they should be provided with appropriate treatment in a timely manner and that treatment should continue until these symptoms abate.

It has been suggested that CRF antagonists (medications that block the actions of CRF and thereby reverse or prevent HPA hypersecretion and enhanced negative feedback of cortisol on the HPA axis) may be a useful treatment for PTSD (Friedman et al., 2000, p. 97). However, such agents are just beginning to be tested experimentally for use in hypertension and have not yet been evaluated in PTSD populations.

To date there have been no studies documenting correction of HPA or any other PTSD-related psychobiological abnormalities following provision of psychosocial or pharmacological treatment, although antidepressants have been found to increase glucocortocoid receptor density in lymphocytes of non-PTSD populations (Sallee et al., 1995). Such physiologic changes in response to a particular treatment would provide a compelling reason to preferentially select that treatment modality. It is hoped future treatment outcome research will assess these variables.

HIPPOCAMPUS AND CORPUS COLLOSUM

Normal Stress Response

As noted earlier, the hippocampus is part of the limbic system that is involved in memory and emotional information processing. The hippocampus is more involved in object rather than emotional memory, whereas the amygdala is more involved in emotional memory (Eichenbaum & Cohen, 2001). The corpus collosum communicates information between the right and left cerebral hemispheres of the brain and is important in integrating perceptions, cognitive processing, and responses.

Functioning in PTSD

In excess, cortisol is toxic to many brain areas, including the hippocampus. Elevated levels of cortisol can lead to accelerated death or delayed development of neurons. Adults with PTSD related to combat or childhood sexual abuse have been shown to have decreased hippocampal volume compared to normal controls (Bremner, Randall, Scott, & Bronen, 1995; Bremner et al., 1997). It is presumed that, even if these adults had low cortisol levels at the time they were evaluated, at an earlier stage of their PTSD they had chronically elevated cortisol levels, which led to hippocampal damage. However, PTSD is also associated with increased risk for drug and alcohol abuse. Because alcohol is highly toxic to the hippocampus (as well as other brain areas), it is possible that some proportion of the decreased hippocampal size may be due to alcohol toxicity rather than abnormally high levels of cortisol. Few neuroimaging studies of adults with PTSD have adequately controlled for lifetime alcohol use, so the relative contributions of these factors remain unclear. It is also possible that smaller hippocampi could be a risk factor for developing PTSD rather than the other way around. At least one study (Bonne et al., 2001) did not find longitudinally decreased hippocampal volume 6 months after trauma, nor did this small study find that smaller hippocampal volume was a risk factor for developing PTSD.

More longitudinal studies are needed in this regard.

Children with PTSD have been found to have significantly smaller intracranial volume (i.e., smaller brains) than a very carefully evaluated control group (DeBellis, Keshavan, et al., 1999). This study did not find decreased hippocampal volume relative to total brain size in maltreated children with PTSD versus the control children. Three alternative explanations have been suggested for this discrepancy between adults and children. It is possible that the hippocampal damage seen in adults is secondary to alcohol abuse and the increased risk for alcohol abuse in adolescence or adulthood had not yet affected the child sample (DeBellis et al., 2000). Alternatively, hippocampal damage may depend on the length of time PTSD has been present, or it may only occur at a later developmental stage than childhood.

In the same research study . . . DeBellis, Keshavan, et al. (1999) also found corpus collosum area to be significantly smaller in maltreated children with PTSD than in the control children. These findings are particularly concerning because corpus collosum area, intracranial volume, as well as the IQ of these children were all negatively correlated with the duration of the child's maltreatment (i.e., the longer the maltreatment, the smaller the brain and corpus collosum and the lower the child's IQ).

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Clinical Significance

These findings provide additional evidence that traumatization can literally be toxic to children's normal brain development and reemphasize the critical importance of prevention, early identification, and effective early interventions for child maltreatment and other forms of child victimization. Such efforts may prevent, minimize, or even reverse the detrimental effects on brain development. It is important to evaluate whether such treatments can in fact reverse or halt such damage; none have been proven to have this effect to date. Because alcohol abuse is in itself toxic to the brain, and chronic PTSD is a risk factor for using drugs and alcohol, early intervention to treat PTSD may also lessen the risk of alcohol-related brain toxicity in traumatized children.

SEROTONIN SYSTEM

Normal Stress Response

Serotonin (5-hydroxytryptamine, or 5-HT) is another neurotransmitter involved in the normal stress response, although its exact mechanism of action is unclear. It appears that 5-HT affects cortisol output in a pathway that is independent of the rest of the HPA axis. Specifically, the serotonergic medication citalopram (Celexa) increases circulating cortisol levels in

the blood, but it is not clear whether this cortisol is released from the adrenal cortex or another site (Seifritz et al., 1996). The raphe nuclei in the brainstem are the primary sites of 5-HT neurons, which connect to the hypothalamus, amygdala, prefrontal cortex, and other brain and spinal cord areas. The 5-HT system is interdependent with the adrenergic system: Both NE and 5-HT modulate anxiety, depressive, and aggressive symptoms, although it appears that only 5-HT regulates obsessive-compulsive symptoms. In addition, new evidence suggests that 5-HT can actually promote neurogenesis (the development of new brain cells) and promote neurotropic (neuron-growing) factors, which improve the functioning of the dendrite portion of the neuron (Charney, 2001; Nester & Duman, 2001).

Functioning in PTSD

Low 5-HT levels are known to be associated with many symptoms commonly seen in PTSD, including aggression, suicidality, obsessive and compulsive symptoms, and depression. It has been postulated that 5-HT may play a role in the development of depression in people who have preexisting PTSD. Adult males with combat-related PTSD have evidence of decreased 5-HT functioning (Spivak et al., 1999), and an agent that blocks 5-HT action was found to worsen PTSD symptoms in some adults with a PTSD diagnosis (Southwick et al., 1997). The strongest evidence implicating 5-HT in PTSD is the efficacy that serotonergic medications have demonstrated in decreasing PTSD symptoms. These medications began to replace the TCAs in the early 1990s, as it became clear that the 5-HT agents had equivalent efficacy in treating adult depression and a more favorable side effect profile. Consequently, they were prescribed for other disorders in which TCA had previously been used, such as panic disorder and generalized anxiety disorder and, eventually, PTSD. Their efficacy has been found to be superior to other pharmacologic agents for PTSD in adults (Friedman et al., 2000).

Clinical Significance

There are currently several medications that increase 5-HT availability in the brain by blocking 5-HT reuptake (the SSRI). Nefazodone (Serzone) is another serotonergic agent that acts through a more complex mechanism. Three SSRI medications, peroxetine (Paxil), fluoxetine (Prozac), and sertraline (Zoloft), have been found to be efficacious in improving adult PTSD symptoms. It is presumed that this effect is due in part to their serotonergic effects, although as noted earlier, they also decrease DA release. Given the suggestion that 5-HT may promote neuronal growth, and the fact that PTSD is now known to contribute to retardation of brain development in children, there is likely to be a great deal of enthusiasm for using serotonergic agents for treating childhood PTSD. In fact, in spite of the lack of research on the effectiveness of SSRI medications for treating childhood PTSD, two recent national surveys have indicated that they are the preferred pharmacologic treatment for this population (Cohen, Mannarino, & Rogal, 2001; Foa, Davidson, & Frances, 1999). More research is clearly warranted in this regard.

ENDOGENOUS OPIATE SYSTEM

Normal Stress Response

Given the suggestion that 5-HT may promote neuronal growth, and the fact that PTSD is now known to contribute to retardation of brain development in children, there is likely to be a great deal of enthusiasm for using serotonergic agents for treating childhood PTSD.

Stress stimulates the release of endogenous opiates (endorphins) from opiate receptors located in the substantia nigra and mesolimbic sections of the central gray matter of the brain. These endorphins produce analgesia to pain and also act to inhibit the release of NE from the locus ceruleus, thus promoting a return to homeostasis. Under normal stress, endorphin release parallels cortisol release because beta-

endorphin and ACTH are both produced from the same substrate (POMC).

Functioning in PTSD

Psychic numbing and avoidance of traumatic reminders are core symptoms of PTSD. Adult veterans with PTSD were found to have diminished sensitivity to pain during exposure to traumatic reminders than at baseline, which was reversible with the opiate antagonist naloxone (Pitman, van der Kolk, Orr, & Greenberg, 1990). In addition, endorphin levels in the brain were found to be elevated in combat veterans with PTSD (Baker et al., 1997). It has been suggested that these elevated levels of endorphins in the brain may cause or contribute to the numbing and avoidance associated with PTSD. It has specifically been suggested that self-injurious behaviors may be related to a dysfunction of the endogenous opioid system; that is, abnormally high endorphin levels may lead to an uncomfortable degree of numbing, which one may try to reverse by inflicting pain on oneself (Herman et al., 1989). No studies have yet evaluated endorphin levels in traumatized children.

One recent study suggests that opiates may be helpful in preventing the development of acute PTSD symptoms in burned children. Saxe et al. (2001) demonstrated that in this population, opiate dosage was negatively correlated with later PTSD symptoms. Thus, opiates may have a protective function early in the course of trauma yet may, in chronic excess, worsen numbing symptoms.

Clinical Significance

Self-injurious behavior (particularly self-cutting, scratching, carving, and so forth) is increasingly seen in traumatized children and adolescents. Anecdotal reports indicate that adolescents in particular use these behaviors as a method of reversing numbing and dissociative symptoms ("it helps me feel again"). An intriguing possibility is that an opiate antagonist such as naltrexone, by blocking the action of endorphin, may be useful in decreasing self-injuring behaviors in children with PTSD symptoms. Although no studies have examined this hypothesis in this population, a few studies have evaluated the use of naltrexone in treating self-injurious behaviors in children with autism. In one study, although naltrexone had no effect on core autistic features, it significantly decreased self-injurious behaviors compared to placebo and, notably, when the medication was discontinued, the self-injurious behaviors increased again (Campbell et al., 1993). Although the mechanisms of self-injurious behavior in autism and PTSD may be different, this may be a promising area for further research and may provide an effective intervention for one of the most concerning symptoms associated with childhood trauma.

THE IMMUNE SYSTEM AND PHYSICAL HEALTH

Normal Stress Response

As discussed above, normal stress leads to an increase in cortisol output from the adrenal gland, which results in suppression of the normal immune response and inflammatory reactions. Stress also causes an increase of NE release from the locus ceruleus, which independently suppresses the immune system by decreasing natural killer cell activity and decreasing production of Immunoglobulin A, cytokines including interferon, and several other cells involved in the normal immune response. This is adaptive in the short term, as one would prefer to expend energy on fighting or escaping danger rather than on mounting an immunologic response. However, if stress becomes chronic, these mechanisms can become problematic by causing chronic high blood pressure, peptic ulcer disease, atherosclerotic heart disease, and immune dysfunctions.

Functioning in PTSD

There is evidence that adults with PTSD have an increased incidence of physical illnesses and medical care utilization (Friedman & Schnurr, 1995). Self-medication of PTSD symptoms can also lead to drug and alcohol abuse, which can

further compromise physical wellness. Because the effect of PTSD on the immune system is primarily mediated by cortisol, it is not surprising that studies of immune function in adults with PTSD have produced contradictory results, with some indicating chronic immune system activation and others indicating suppression of immunologic activity. One study of sexually abused children (DeBellis, Burke, Trickett, & Putnam, 1996) found that these children had indications of abnormal immunologic function. This may explain the increased incidence of somatic complaints in these children.

Clinical Implications

There is significant evidence that relaxation techniques such as meditation can reverse many of the physical symptoms associated with stress in adults and that these changes may be mediated by normalization of immunologic function. The field of psychoneuroimmunology is dedicated to explicating these interactions and how psychological interventions may decrease the negative impact of stress on physical functioning. Little research has been done with children in this regard, but these adult findings suggest that relaxation techniques may be beneficial for children with a preponderance of somatic complaints. The fact that abuse may impair immune functioning over time is another compelling reason to offer early treatment to maltreated children.

IMPLICATIONS FOR PUBLIC POLICY AND FUTURE RESEARCH

In addition to the clinical implications discussed throughout this article, our current knowledge about the psychobiology of PTSD has important policy and research implications. First and foremost, evidence is mounting that childhood traumatization can be harmful to normal brain development and functioning. This emphasizes the importance of preventing child victimization, providing better screening and earlier identification of children who have experienced traumatic life events, and developing and providing effective interventions for these children in a timely manner. Several public policy initiatives may be essential for implementing these improvements.

Ideally, we need to identify more effective ways of preventing child maltreatment. Interventions such as targeted home health visitation (typically starting prenatally and continuing for several months to years) have garnered some evidence of efficacy in decreasing rates of child abuse (MacLeod & Nelson, 2000). Ongoing innovative prevention efforts that rigorously measure outcomes should be encouraged through adequate funding at the state and federal level.

Second, consideration should be given to routinely screening children for traumatic exposure and related symptomatology, whether in the pediatric, school, or some other widely available setting. Although several relatively brief self- and parent-report instruments are available in this regard, use in routine settings may require that even shorter instruments be developed and validated for such use. There will undoubtedly be resistance to implementing such screening, in part due to lack of time or resources in pediatric or school settings. There may also be resistance based on legal issues; that is, concerns about confidentiality, the optimal way to obtain child and parental consent for screening, and how to proceed if such consent is denied. Failure to report identified child abuse to a child protective agency or failure to refer symptomatic children for appropriate services may lead to legal liability. These issues are legitimate and complex and need to be addressed in a systematic way before widespread screening can be expected to occur.

Finally, although significant progress has been made in developing effective treatments for traumatized children, much remains to be accomplished in this regard. Several studies have demonstrated the efficacy of trauma-focused CBT for this population, but we have yet to identify the "critical elements" of this treatment approach or an optimal length of time over which it should be provided; research is needed to clarify these issues and perhaps to identify factors that may predict the need for more intensive or longer treatment in some children. Most CBT treatment studies in traumatized children have focused on victims of child

abuse, and it is not clear that this is the optimal treatment for children exposed to other types of trauma. In addition, some children do not respond to CBT; alternative treatments must be developed and empirically tested for such children, especially those with comorbid psychiatric conditions including substance abuse disorders, and those in living in highly dysfunctional families or out-of-home placements. Particularly given the evidence discussed in this article that suggests that a variety of medications may be important in improving symptoms and normalizing brain functioning in traumatized children, and the fact that many physicians are prescribing medication for these children, it is concerning that there has not been a single well-controlled medication treatment trial for childhood PTSD. Scientifically rigorous studies of this type are greatly needed. More studies of basic neurobiology and longitudinal neuroimaging studies may contribute greatly to suggesting innovative treatments for this population.

Particularly given the evidence discussed in this article that suggests that a variety of medications may be important in improving symptoms and normalizing brain functioning in traumatized children, and the fact that many physicians are prescribing medication for these children, it is concerning that there has not been a single well-controlled medication treatment trial for childhood PTSD.

All of these research endeavors depend in large measure on federal funding, and there is presently no governmental funding source dedicated to child trauma research. We applaud recent efforts by the National Institute of Mental Health to direct resources to the area of child traumatization, through both intramural and extramural channels, and hope that these resources continue to be made available. In addition, the Substance Abuse and Mental Health Services Administration has recently funded a National Child Traumatic Stress Initiative, which will, it is hoped, encourage more research in this regard.

Developing and testing effective treatments for traumatized children will have little impact if these treatments are not readily available to the families in need of them. Thus, there is a need to improve the availability of high-quality, specialized training of professionals treating these children. At least one state is currently taking the initiative to develop treatment guidelines in this regard and to provide specialized training to mental health providers (California Task Force Guidelines for Treatment of Child Trauma Victims, 2001). Several professional organizations have dedicated training workshops or institutes to this type of training as well. Last year, the training requirements for child psychiatry residency programs for the first time included a requirement of "instruction in the recognition and management of domestic and community violence as it affects children and adolescents, (including) physical and sexual abuse as well as neglect" (American Medical Association, 2001, p. 328). These are all positive developments that should be continued and expanded on.

However, several disturbing trends may currently or in the future detract from the availability of optimal treatments. First, increased managed care restrictions have frequently resulted in fewer mental health treatment sessions being approved, higher copayments required for each treatment session, and unavailability or lack of therapists on approved provider panels with the appropriate expertise in treating traumatized children. Managed care has also typically differentially paid for physician versus therapist visits in a manner that virtually ensures that many children will receive pharmacotherapy rather than psychotherapy. This obviously is contradictory to our current knowledge about effective treatments for traumatized children, which indicates the appropriateness of providing CBT interventions to these children. Second, as a result of the Balanced Budget Act of 1996, funding for Child and Adolescent Psychiatry residency training programs has been cut in half, resulting in closure or downsizing of programs that train physicians in this specialty. This has occurred despite the fact that child psychiatry has been identified as a specialty with

too few providers to meet the clinical needs of children in the United States (American Academy of Child and Adolescent Psychiatry Legislative Action Alert, 2001). Because child psychiatrists are the most appropriate physicians to conduct research on and prescribe psychotropic medications for traumatized (and other) children, this development is likely to hamper efforts to further our knowledge about the potentially promising medication treatments discussed above. It may also contribute to the disturbing findings that currently, most psychotropic medication prescriptions for children are written by nonpsychiatrists, and many of these appear to be prescribed inappropriately (Angold, Erkanli, Egger, & Costello, 2000; Zito et al., 1999). Thus, to optimize treatment of traumatized children, it will be important to increase both insurance coverage of mental health treatment and funding for training child psychiatrists.

CONCLUSION

Recent research regarding the neurobiology of PTSD has provided us with growing evidence of the negative impact traumatic life events have on childhood brain development and functioning and has suggested intriguing therapeutic possibilities for traumatized children. It has also emphasized the importance of early identification and treatment for such children. More research is needed to test these potential treatments, particularly pharmacologic therapies, alone and in combination, for children with a variety of trauma-related symptoms. Additional efforts are needed to provide training in those interventions that already have evidence of effectiveness. Several changes in policy and funding are suggested to optimize treatment for traumatized children.

IMPLICATIONS FOR PRACTICE, POLICY, AND RESEARCH

- Trauma prevention, early identification, and efficacious treatment are critical in protecting symptomatic traumatized children from developing significant psychobiological abnormalities.
- Ongoing federal funding of neurobiological trauma research and research into effective trauma treatments are needed to provide optimal care for traumatized children in the future.
- Policy changes, including establishing true parity for mental health interventions and restoring federal funding for child psychiatry training, are needed to provide optimal services to traumatized children.

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SUGGESTED FUTURE READINGS

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